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FEASIBILITY OF COMMERCIAL SPACE MANUFACTURING - PRODUCTION OF PHARMACEUTICALS
Volume I: Executive Summary

By McDonnell Douglas Astronautics Company
Saint Louis Division
Saint Louis, Missouri 63166

Final Report

November 9, 1978

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16. ABSTRACT

This report describes the study results achieved over two periods of related activity, June - December 1977 and March - October 1978. It is organized in three volumes to meet the needs of different audiences. The first, an executive summary, serves as an overview aimed at those responsible for committing public and private resources to new ventures. The second recounts the activities of the study and presents fundamental lessons learned. This volume is intended to serve two groups: those in the aerospace industry who may wish to have a model for their efforts to attract participation in space processing by other industries; and those in non-aerospace industries who want to learn more about the possibilities of space processing. The third volume contains the detailed product data collected and reviewed to support the activities in Volume II.

The report summarizes the study by identifying the lessons learned during the course of its execution. Before the enormous potential benefits of space processing can reach the public--the basic goal of NASA's Materials Processing in Space program--industry must be willing to participate in the development of processes. Such investment, however, will not follow until industry itself is made aware of the promise of space processing and is supplied with hard data supporting such promises. It is to this purpose that we have directed our efforts.

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PREFACE

This report describes the study results achieved over two periods of related activity, June-December 1977 and March-October 1978. It is organized in three volumes to meet the needs of different audiences. The first, an executive summary, serves as an overview aimed at those responsible for committing public and private resources to new ventures. The second recounts the activities of the study and presents fundamental lessons learned. This volume is intended to serve two groups: those in the aerospace industry who may wish to have a model for their efforts to attract participation in space processing by other industries; and those in nonaerospace industries who want to learn more about the possibilities of space processing. The third volume contains the detailed product data collected and reviewed to support the activities in Volume II.

The report has been organized to take the reader through the chronology of the study process. Although many of these steps were accomplished simultaneously, we have -- for simplicity and clarity -- organized them into discrete segments, moving first through the plan established to target and contact pharmaceutical companies, then the laboratory work needed to support the expanding company-to-company cooperation and technology interchange, through the literature search and analysis of potential products and finally through the production engineering analysis. The report then summarizes the study by identifying the lessons learned during the course of its execution. Before the enormous potential benefits of space processing can reach the public -- the basic goal of NASA's Materials Processing in Space program -- industry must be willing to participate in the development of processes. Such investment, however, will not follow until industry itself is made aware of the promise of space processing and is supplied with hard data supporting such promises. It is to this purpose that we have directed our efforts.

This report is submitted under NASA Contract Number NAS8-31353. The work was performed by McDonnell Douglas Astronautics Company - St. Louis Division under the direction of William R. Marx and Dr. Ronald A. Weiss, Study Managers during the first and second periods of the study respectively. This contract was administered by the NASA Marshall Space Flight Center, Huntsville, Alabama.

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FOREWORD

As the principal result of this study activity, the McDonnell Douglas Astronautics Company - St. Louis Division, elicited and fostered the participation of several pharmaceutical firms, to varying degrees, in exploring the potential benefits which may accrue from processing pharmaceuticals in space.

One of the conditions for their participation, however, was that the companies not be linked with any potential product or process because of the highly competitive nature of the industry. With NASA concurrence, therefore, and participating company approval, we have deleted the names of any company associated with this study in order to be able to emphasize the important product data and technology interchange achieved with them.

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1.0 INTRODUCTION

The environment of space holds great promise for new manufacturing processes which take advantage of the absence of such earthbound phenomena as natural convection and sedimentation. Using these processes, space manufacturers can not only produce products superior to those produced on the ground, they can produce entirely new classes of products. Though characteristics of space -- including high vacuum and radiation -- can be duplicated on earth, the most important characteristic, weightlessness, can be achieved only for an extremely brief period. In the microgravity of space, molten materials can be suspended without containers -- eliminating a major source of contaminants. More importantly, in space we can escape gravity-induced convection. Convection currents -- which are caused by the thermal gradients in fluids -- can lead to undesirable structural differences in the solid materials produced. Having escaped the problems posed by these currents, space manufacturers will be able to grow crystals of great purity with highly controllable characteristics; they will find it much easier to mix and homogenize liquids, to cast metals, and to separate and purify the elements of mixtures.

The question immediately arises, why is not industry actively pursuing opportunities to develop materials and processes in space? The first reason is that industry is not generally familiar with the potentials of space. NASA and key aerospace organizations are working continually to rectify that situation. The second, and by far the dominant, reason is that observation of basic phenomena with potential application is only the start of the industrial process. A major body of data on applied research into processes and materials characteristics, material applications potential, potential markets and their probable growth, and the characteristics of production systems and logistics must be developed as a vital decision base. Before private industry will invest the money required to begin such untried processes, it must be reasonably confident that the product will have a high value, that the benefits of processing in space will be substantially greater than processing on the ground (i.e., capable of producing less expensive, more useful products, or producing products that cannot be made on earth). The investor must also be reasonably confident: that the space process can be developed in a given time at an affordable cost; that a market exists at a price which assures a reasonable return on investment; and that this market will

not disappear because a new product appears and captures the market, or because a breakthrough in the technology occurs that permits competitive ground production.

Because these risks are so difficult to assess, and because the required initial investment is so large, most industries adopt a "wait and see" attitude. Until more data are available, industries find it extremely difficult to assess the potential of new processes and products.

To address this problem, we approached NASA with a proposal to study the feasibility of commercial manufacturing of pharmaceuticals. The goal of this undertaking was to induce pharmaceutical firms to participate actively, on a continuing basis, in exploring the possibilities of using the unique environment of space to produce new products. The MDAC-St. Louis' approach was, first, to secure the initial commitment of these firms by providing key management and technical executives with preliminary data and forecasts of the business and technical potential of space processing. The second aspect of the approach was to foster the initial commitments by establishing continuing technical and management exchanges with the interested pharmaceutical companies to our mutual benefit.

Our enthusiasm for space processing focused on the promise shown by our company funded efforts with electrophoresis. In order to accomplish the facets of this goal, we had to expand the data base we had developed -- including significant laboratory work and an awareness of the state-of-the-art -- and we had to target companies potentially interested in the benefits of the process.

In our early company funded work with electrophoresis, we learned how to separate relatively large quantities of test materials. We also experienced the adverse effects of gravity on the process -- causing the vertically flowing stream to collapse on itself (if the sample were denser than the carrier fluid) or to ball up and float to the top of the chamber (if the sample is less dense than the carrier fluid). On the basis of these experiences we began developing, with MDAC-St. Louis funds, our own mathematical models of these effects so that we could predict effects of design changes and operating conditions, and ultimately forecast the benefits of operating in space. We also ran company funded preliminary mass balance calculations; these activities assured us that we could define

and demonstrate the types of requirements needed to characterize conceptual space and ground production systems, with their requisite logistics capabilities, in presentations to NASA and industry.

Under the contract, we addressed the problem of targeting pharmaceutical companies. Our first step was to engage the services of Price Waterhouse and Company to provide important drug industry data. The overall drug industry analysis provided by Price Waterhouse included: detailed assessments of the top twenty companies in the industry, focusing on their apparent commitment to innovation, their research and production emphasis on products having high potential for space production, and the prominence of their executives. Price Waterhouse also helped us prepare the presentation to be made to these companies, recommending a "businessman to businessman" approach.

Letters were written to the selected companies. These letters gave an overview of the feasibility study, listed some of the potential benefits to pharmaceutical manufacturing by processing in space, and requested an opportunity to make a presentation. Ten of fourteen companies requested the presentation.

Although the pharmaceutical company personnel were generally skeptical at first, once they understood the benefits of microgravity, the implications of the preliminary results of continuous flow electrophoretic separation, and the potential of an integrated space pharmaceutical production system manufacturing products of great value, they became increasingly intrigued. As a result of these initial contacts, six companies responded positively to our invitation for assistance and cooperation in this study. Two companies agreed to participate actively in the form of laboratory testing a product of specific interest to themselves. Four additional companies agreed to participate in a more passive mode by suggesting products, providing marketing information and reviewing the analysis of results. One of the conditions for their participation, however, was that the companies not be linked with any potential product or process data because of the highly competitive nature of the industry. With NASA concurrence, therefore, and participating company approval, we have deleted the names of any company associated with this study and, instead, emphasized the important product and process information obtained from them.

This report describes our method of obtaining pharmaceutical company involvement, the development of protocols with two of these companies, laboratory results of the separation of serum proteins by the continuous flow electrophoresis process, the selection and study of candidate products, and their production requirements. From the twelve candidate products discussed with, or suggested by, the visited pharmaceutical companies, six were selected for further evaluation; antihemophilic factor, beta cells, erythropoietin, epidermal growth factor, alpha-1-antitrypsin and interferon. Production mass balances for antihemophilic factor, beta cells, and erythropoietin were compared for space versus ground operation. Selection of the best mode of operation for these three representative products permitted a conceptual description of a multiproduct processing system for space operation. Production requirements for epidermal growth factor, alpha-1-antitrypsin and interferon were found to be satisfied by the system concept.

In the technical interchanges that occurred with these pharmaceutical companies, significant data were generated and many valuable lessons were learned. These data and lessons, detailed in this report, are intended to serve others interested in exploring the possibilities of space processing.

2.0 PHARMACEUTICAL COMPANY INVOLVEMENT

The aspiration of this task was to obtain the participation of one or more prominent ethical drug manufacturers in this study and gain their evaluation of product and process commercial feasibility. The industrialization of space, and any resultant social benefits, would not be realized at any early date without the cooperation, endorsement, and initiative of commercial industry. Our approach consisted of an analysis of the drug industry and identification of primary candidate companies for potential study participation. Communications were then established with a number of these companies for the purpose of gaining the assistance of one or more of them in product selection and evaluation.

Selection of potential pharmaceutical company participants was limited to domestic United States ethical drug producers. The task was principally accomplished through subcontract with the St. Louis office of the business consultant firm of Price Waterhouse and Company. This firm has considerable knowledge of the pharmaceutical industry, its key personnel and the environment in which they operate. Their report also included a brief overview of the ethical drug industry and detailed information on the pharmaceutical companies recommended as candidates for presentations. This information included line of business data, results of operations and financial position, specific information concerning ethical drugs currently produced, biographical data on key individuals within the company, and preferred initial contacts at each company. Throughout their consultantship, Price Waterhouse and Company stressed the need for MDAC-St. Louis to initiate our contacts and communicate with pharmaceutical firms strictly on a "businessman-to-businessman" basis. Only in this way could we succeed in establishing the rapport which would permit us to address potential areas of mutual business interest, in a common language and with a mutual understanding of our technical and business goals.

Active producers of ethical drugs were identified through analysis of product line and related business data found in company annual reports, "10-K reports," and other publicly available sources of information. This analysis resulted in the reduction of the initial field of 100 drug firms to 42 potential candidate companies. The 42 candidates for study participation identified during this preliminary

screening process were evaluated in a final screening for the purpose of first selecting, then ranking, the candidates for initial contact. A final list of 20 candidate companies was compiled using several different selection criteria. Among these were quantifiable factors of comparison such as industry sales position, profitability, research and development expenditures, various financial ratios and growth rates. The ten largest pharmaceutical firms (in terms of 1976 consolidated net sales) were included because: 1) prominent names associated with this effort would provide visibility and recognition; and 2) major companies would more likely have the resources to conduct experimentation and initial financial investment. Subjective criteria were utilized as well to evaluate each company's leadership in new product development and other factors including top management commitment to innovation.

This analysis of the 20 candidate pharmaceutical companies revealed that all were potentially acceptable as participants in the study. Once these companies had been identified for contact in rank order of desirability, letters were prepared and sent to each selected company contact. Approximately one week later, follow-up telephone calls were made to each of the company officials to establish dates for formal presentations on pharmaceutical space manufacturing. These follow-up calls were successful in setting up meeting dates with 10 of the first 14 companies. The other four were either already involved with NASA Space Processing or were uninterested in a briefing on the subject. Ten was the maximum number of trips feasible under the study budget.

The formal presentation was organized into two principal sections. The initial section of the briefing established the meeting's objective, described MDAC-St. Louis' product line and involvement in space and defined the NASA space program and objectives. It also outlined the programmatic importance of early involvement of drug industry participants to assure the success of commercial space development. The second section of the presentation described technical and business objectives of the pharmaceutical study and the process system concept; described in detail the MDAC-St. Louis' in-house experimental work accomplished to date on continuous flow electrophoresis for use in space bioprocessing; defined the benefits of space improved biological separation; and identified candidate products for space processing.

A series of vu-graphs were developed to support the formal presentation. In addition, brochures incorporating these vu-graphs were prepared for distribution at the conclusion of each drug company presentation. This brochure allowed the drug company participants to review the material at their leisure after the formal presention, discuss it with their colleagues and come to a conclusion about further participation.

Typically, the officials of each pharmaceutical firm were initially skeptical of the benefits of space processing, but they were willing to listen. Following the description of the MDAC-St. Louis laboratory experiments of continuous flow electrophoresis and how microgravity may enhance the separation of cells or protein substances in such a continuous flow electrophoresis system, most of the technically oriented officials perceived the potential capability of space processing to produce higher purity and/or unique pharmaceutical products. Discussions concerning this subject were fruitful and generally resulted in allaying of initial skepticism.

Several significant accomplishments were achieved by these meetings. Probably the most far reaching action was making the technical people present at these meetings aware of the effects of gravity in their current and future chemical processing activities. Another major accomplishment was making these corporate decision makers aware of the existence of a space program in which they could participate for the benefit of their company. They were under the impression that the space program was conducted primarily for astronomical research, political and military reasons. The characteristics of space applicable to both a research and manufacturing environment had never been elucidated for them until the formal presentation.

During the course of this study six of the ten companies contacted agreed to participate. Of the six, two companies agreed to participate actively in the form of laboratory testing a product of interest to themselves. The four other companies agreed to participate in a different mode by suggesting products, providing marketing information and reviewing the analysis of results. Several weeks after the formal presentation, a seventh company informed us that they had started investigating the space processing feasibility of four products of interest to

them. They indicated that the results of this activity and a formal corporate decision to participate in the MDAC-St. Louis study would take time. During the course of this study, however, no formal comment to participate was forthcoming. Three of the companies contacted chose not to participate.

The approach taken to obtain drug company participation in the study resulted in the establishment of communications with the drug industry and general expressions of interest. The reasons for this success are many, but of greatest importance was the contribution of the in-house MDAC-St. Louis continuous flow electrophoresis laboratory test results to the basic understanding of the potential benefits of microgravity to the pharmaceutical industry. Other reasons include: 1) an obvious commitment of MDAC-St. Louis to the program; 2) careful selection of contacts; and 3) the fact that no immediate financial commitment was required of the drug company participants. Their initial willingness to listen to the presentation was probably tempered by curiosity about why MDAC-St. Louis was seriously considering space processing of pharmaceuticals. Also, an influence could be the decreasing number of new pharmaceuticals being introduced; any process or concept which could produce multiple new and innovative products must be investigated.

The reasons why three companies have decided against participation are generally related to a combination of the extremely long development time frame (10-15 years), long term commitment with unanswered proprietary right retention questions, and the competition from alternative products and processes for limited corporate research and development resources. This latter factor was of paramount importance in two companies' responses.

The principal conclusion to draw from the decision of the three drug firms not to participate in the study is that despite its promise, not enough is known about potential space processed products to allow solid forecasts of how they would compete with other currently promising product alternatives which can be developed along more traditional lines.

3.0 SUPPORTING LABORATORY DATA

Prior to entering into this study for NASA, considerable work was conducted with a first generation electrophoresis chamber during which methods were established to study the effects of gravity on the free flow electrophoresis process. These studies showed, among other things, that protein and cell samples whose specific gravities varied significantly from that of the carrier buffer could not be processed at flow rates required to separate materials having small differences in electrophoretic mobility. These data, documented in previous MDC publications, were used to demonstrate to the drug companies that laboratory test data were available concerning proteins and cells which illustrate the limit that gravity does impose on their processing by free flow electrophoresis.

The initial interactions with pharmaceutical companies stimulated several of them to participate in the study to various degrees. Two companies in particular wished to cooperate with us in developing a better understanding of products of interest to them. A series of follow up meetings with laboratory personnel from both MDAC-St. Louis and the participating drug companies ensued. The choice of material to be tested, assays to be used and the frequency of testing were established. Protocols were prepared based on previous MDAC-St. Louis company funded research, the capabilities of the laboratories, logistics of sample transport, and company policies concerning management of proprietary data. One of the major considerations of the protocols was control of the release of information. The protocols emphasized that the pharmaceutical company would have final say as to how the data would be represented.

During this contract, however, interlaboratory testing was accomplished with only one company. The time involved in developing joint protocols, obtaining product standards and our familiarization with new assay procedures for the products suggested by the second participating company did not allow sufficient time in this contract to obtain electrophoretically separated product data for this report.

A data base concerning AHF VIII and other blood components was developed upon which MDAC-St. Louis established a technology interchange with the participating pharmaceutical companies. As a result of this exchange, a preliminary characterization of AHF VIII and other important blood components by free flow electrophore-

sis was accomplished. This, in turn, we believe, has enhanced the level of interest of those companies in the potential offered by processing pharmaceuticals in space. Initial interlaboratory tests with the pharmaceutical company were conducted with cryoprecipitate as a starting material. Protein assays and clotting times on the electrophoretically separated cryoprecipitate were initially conducted at MDAC-St. Louis. Early tests in which the separated samples were sent to participating companies for antigen assays showed deterioration due to problems associated with logistics. The cooperating company recommended and assisted MDAC-St. Louis in establishing an MDAC-St. Louis capability to carry out the required antigen assays eliminating delays and other factors tending to compromise test results. During these early cooperative tests we determined that the many variabilities of cryoprecipitate made it unsuitable as a research tool for free flow electrophoresis. It remains, however, a viable candidate for space bioprocessing since these variabilities would be insignificant in large scale processing.

As a consequence, the more uniform, commercially available antihemophilic factor VIII, Hemophil^{R}, was chosen for laboratory testing. Samples were prepared by dissolving 0.7 mg of Hemophil^{R} in 0.0025M diethylbarbituric acid/sodium diethylbarbiturate, pH = 8.3. The same buffer was used as the carrier fluid for the electrophoretic separation. A typical separation of Hemophil^{R} is shown in Figure 1. Samples collected during sample streaming with no voltage applied to the chamber showed that all protein materials were exiting through tubes 19 and 20 of 96 outlet tubes. When an electrical field strength of 48 volts/cm was applied across the width of the chamber and allowed to stabilize for 30 minutes, samples were collected in tubes 20 through 56. Each tube was analyzed for total protein, AHF VIII clotting activity and AHF VIII antigen activity.

The results of these runs showed that AHF VIII migrated in the electric field and that the antigen moiety and the bulk of the clotting moiety moved with the fastest moving protein peak. AHF VIII can be separated from a portion of the unwanted proteins found even in the most highly purified commercial preparations. This is of interest to the pharmaceutical companies because additives (required in their purification procedure, and which may cause toxic side effects) are not needed in the electrophoresis process. Although molecular dissociation of AHF VIII occurs, the clotting properties are still intact. Since the patient with classic hemophilia lacks only the clotting moiety, its dissociation is not a deterrent to

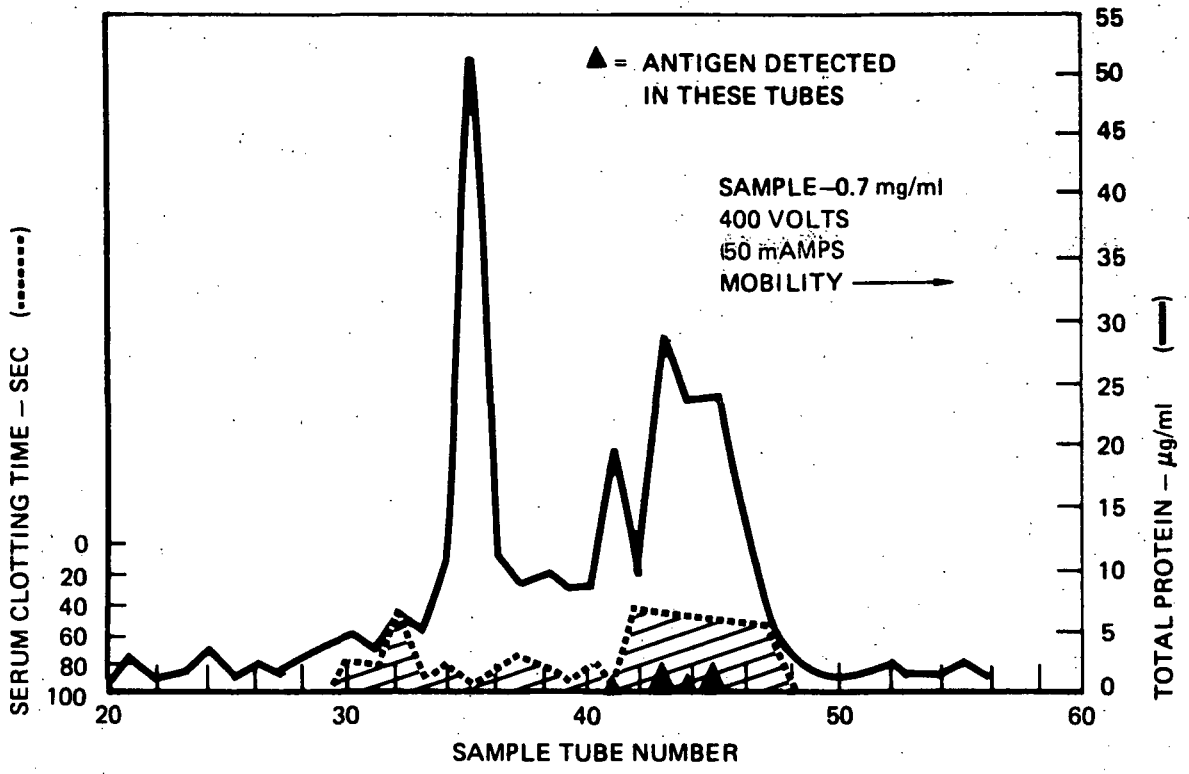


Figure 1. Electrophoretic Separation of AHF VIII

further investigation of this product. Both participating pharmaceutical companies expressed interest in a purified clotting moiety as a possible product. A small amount of highly purified, slow moving material showing clotting activity was noted in typical AHF VIII separations of Hemophil^{R}. This fraction is of particular interest to one of the companies since it provided a unique form of clotting materials which could be used to study AHF VIII by new immunological techniques.

One sample sent to the participating laboratory was concentrated at MDAC-St. Louis by lyophilization. The resultant rehydrated sample contained no antigenic activity, indicating the possible removal, during processing, of a cryoprotective material. We are now investigating this loss of activity in-house by recombining several separated fractions. This finding highlighted the logistical problems to be encountered in transporting materials from one laboratory to another for conducting specialized tests. It emphasizes the need for MDAC-St. Louis to establish a broad base biological capability for complete in-house product evaluation of separated materials.

As an adjunct to the contractual studies, MDAC-St. Louis conducted company funded research on the electrophoretic separation of normal human plasma. A typical separation is shown in Figure 2. It may be possible to obtain all of the important blood fractions of medical importance in purified form in a single continuous process. Gamma globulins, used to protect against bacterial and viral diseases, are slow moving materials whereas albumin, used as a plasma expander, is very fast moving. These materials are currently obtained commercially by precipitation methods, but in such methods many important components, such as AHF VIII, other clotting factors, alpha antitrypsin, etc., may be neglected, lost or denatured by the process. We are currently developing assays to qualitatively and quantitatively identify these individual components and their position in the separation field. Figure 3 presents an example of purified fibrinogen mobility in the MDAC-St. Louis instrument. Under the same chamber operating conditions, the fibrinogen peak is apparently present in the same collecting tubes (37 through 40) in both the normal plasma sample and the purified fibrinogen sample.

A process in which all blood components can be obtained in a single step is of significant interest to both participating companies from the standpoint of economics as well as expansion of their product line.

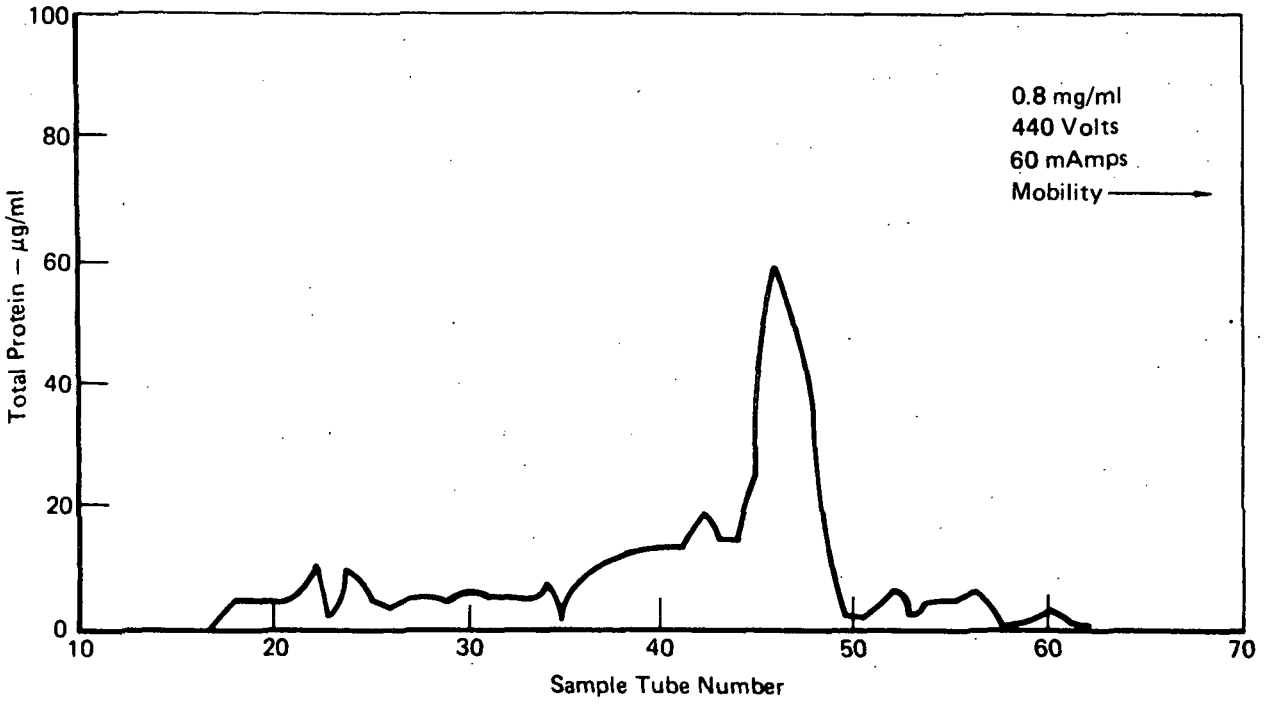


Figure 2. Human Plasma Electrophoresis

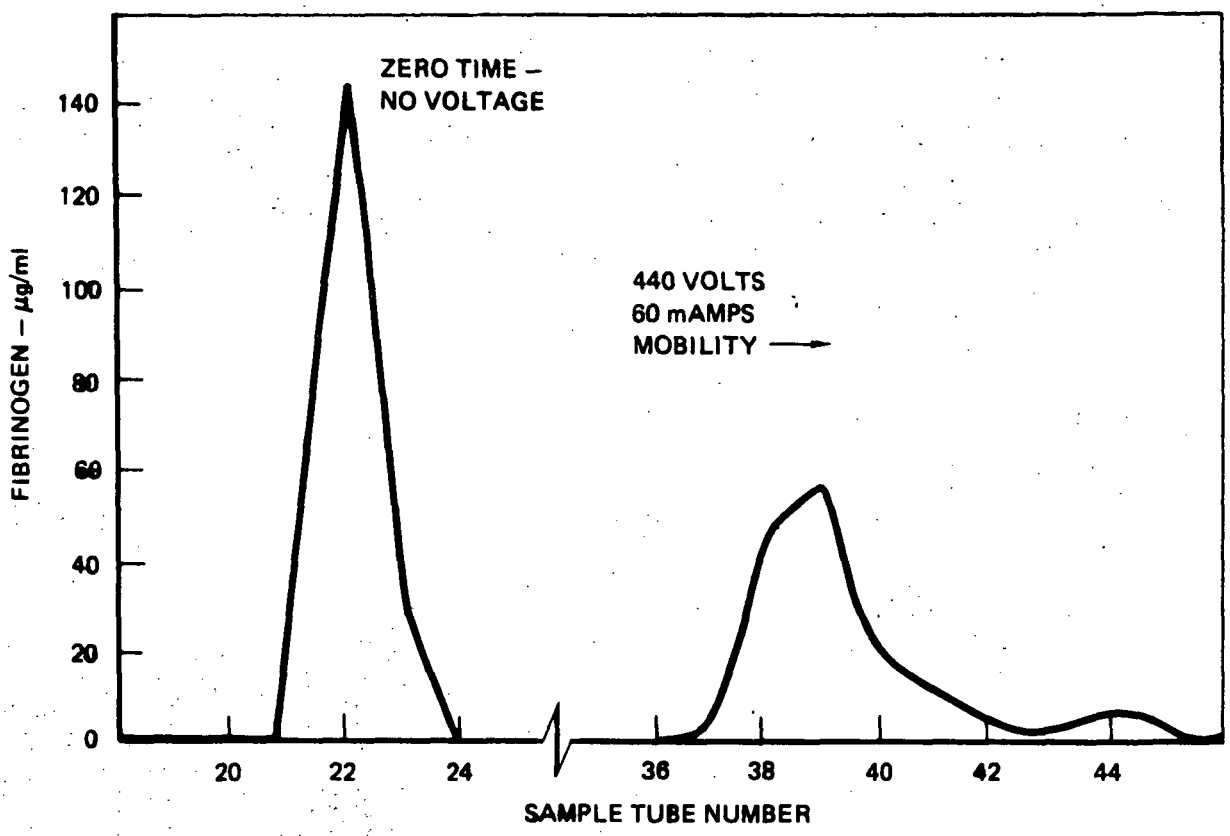


Figure 3. Human Fibrinogen Electrophoresis

4.0 PRODUCT EVALUATION

There is almost an unlimited number of candidate biological products from humans, animals and plants, that potentially can be improved by space processing. It is only necessary, however, to show that one or more materials can be beneficially produced in space. Thus, a selective evaluation of candidate products is very desirable so that sufficient in-depth analysis can be performed on promising candidates.

From a list of candidate products identified in previous studies or suggested in discussions with the pharmaceutical industry and the medical and academic communities, twelve products were selected for in-depth evaluation. Technical, medical and economic data were collected for each product. A synopsis of these data is shown in Figure 4. These data permitted a selection of six of these products to serve as "models" for an additional market analysis to determine the commercial viability of their being processed in space. The six products were chosen on the basis of a "humanitarian value index" which took into account the number of patients, severity of the disease to be treated, potential space improvement to the manufacturing process, competitive products and the production facility requirements. Using this index as a guide, the six products selected were alpha-antitrypsin (A-AT), antihemophilic factor (AHF), beta cells, erythropoietin (ESF), epidermal growth factor (EGF), and interferon.

Alpha-antitrypsin is a protein found in human blood that inhibits the destructive action of the enzyme trypsin. It is believed that the uncontrolled presence of trypsin in the lungs results in tissue damage producing emphysema. According to our estimates, approximately 100,000 people in the United States severely afflicted with this disease demonstrate abnormally low levels of A-AT in their blood. The commercial scale isolation and purification of A-AT through space processing may provide the first pharmacological approach to containing the damage of emphysema due to this enzyme deficiency.

Antihemophilic Factor VIII (AHF) is one of the 13 clotting factors present in the blood. Since each factor works in sequence for clot formation, lack of any one factor will result in bleeding. An AHF VIII deficiency, hemophilia A, is about 5-10

PRODUCT	PATIENTS	TREATMENT	COST/DOSE	STARTING MATERIAL	FINISHED PRODUCT
ANTIHEMOPHILIC FACTOR	20,000	1200U/DOSE: EVERY 2 DAYS SEVERE; ONCE/WEEK MILD	$132	PLASMA; CRYOPRECIPITATE	LYOPHILIZED POWDER
IMMUNO-GLOBULINS	300,000	4mg-5000mg/DOSE	0.3¢/mg	PLASMA	LYOPHILIZED POWDER
GROWTH HORMONE	1,500	4U/DOSE: 3 TIMES/WEEK	$15	FROZEN PITUITARY	LYOPHILIZED POWDER
UROKINASE	1,000,000	350,000U/DOSE: 14 DOSES/ TREATMENT	($400 EST)	URINE, FROZEN KIDNEY	LYOPHILIZED POWDER
ERYTHROPOIETIN	1,050,000	1600U/WEEK; LIFE	N/A($1325 EST)	URINE, FROZEN KIDNEY	LYOPHILIZED POWDER
BETA CELLS	3,200,000	300,000 CELLS/DOSE	N/A($200 EST)	FROZEN PANCREAS	FROZEN CELLS
ALPHA-ANTITRYPSIN	100,000	25mg/kg: EVERY 4-6 DAYS	0.2¢/mg	PLASMA	LYOPHILIZED POWDER
EPIDERMAL GROWTH FACTOR	14,000	20ng/cm^2 burn: DAILY FOR 7 DAYS	($50/mg EST)	SUBMAXILLARY GLAND CULTURE	LYOPHILIZED POWDER
INTERFERON	100,000,000	3×10^6 UNITS DAILY FOR 30 DAYS (VARIES WITH DISEASE)	($1/$10^6$ UNITS EST)	LYMPHOCYTE CULTURE	LYOPHILIZED POWDER
TRANSFER FACTOR	535,000	0.1-0.2 UNITS WEEKLY	N/A($25/ UNITS EST)	LEUKOCYTE CULTURE	LYOPHILIZED POWDER
SOMATOMEDIN	123,000,000	0.5mg/40kg 3 TIMES/WEEK	N/A($1 EST)	PLASMA	LYOPHILIZED POWDER
GRANULOCYTE STIMULATING FACTOR	500,000	2.5×10^8U: 3 TIMES/DAY	N/A($100 EST)	LUNG CULTURE	LYOPHILIZED POWDER

Figure 4. Product Data Summary

times more prevalent than the reduction or absence of any other clotting factor. This deficiency affects more than 20,000 Americans, mostly males, and can be kept under control by replacement therapy. It is of interest primarily because some of the hemophiliacs develop antibodies to current preparations and because hepatitis virus is a hazardous contaminant that is not always detected. Higher purification may eliminate these problems. It is also of significant interest in that up to 9 million of the 12-13 million pints of blood collected annually in this country may be used to produce AHF VIII for these approximately 20,000 patients. Newer methods, such as continuous flow electrophoresis, could recover other products, now lost, to meet other medical needs.

Beta cells in the pancreatic islets of Langerhans produce a hormone known as insulin. The physiological function of this hormone is to aid in the regulation of carbohydrate metabolism. A deficiency in production of this hormone results in diabetes mellitus, often called "juvenile onset" or "insulin dependent" diabetes. The present United States population of known insulin dependent diabetics is believed to be 1.5-3 million people concomitant with an additional 3.5-7.0 million adult onset diabetics who may eventually require insulin as their disease progresses. While daily injections of insulin can sustain the patient's life, it does not eliminate all the other pathology associated with diabetes. It is anticipated that a single injectable transplant of human beta cells may provide a surrogate pancreas and thus eliminate the need for further insulin injections.

Epidermal growth factor is a protein produced in the submaxillary glands. It has the fundamental property of stimulating the production of ectodermal (skin origin) tissue. In clinical situations where the skin is damaged by burns and wounds of various types, application of EGF to the damaged areas could result in their rapid restoration to normal function. This substance also has a trememdous potential for both supplementing and partially replacing fetal animal serums in tissue culture systems.

Erythropoietin stimulates red blood cell production in the bone marrow. This protein hormone is a product of specific kidney cells, and chronic renal failure can result in an anemic condition. Patients on kidney dialysis are especially in need of this hormone since their kidney may no longer produce ESF and only blood

transfusions can replace the red blood cells lost after their normal 120 day life cycle.

Interferon is a protein substance produced by blood lymphocytes and fibroblasts challenged by a virus. This interferon offers temporary immunity to other body cells against most challenge viruses when subsequently attacked. Preliminary human clinical trials indicate this natural body product has great therapeutic potential against many diseases of viral or suspected, but not proven, viral origin such as cancer. It is probably one of the most sought after candidate products today with about one hundred pharmaceutical companies and universities actively conducting research and development related to its potential therapeutic commercialization.

Each of these products allows evaluation of a processing system in a different mode. AHF and A-AT are contained in a protein mixture from blood plasma and would utilize a protein electrophoresis system for separation; both ESF, the product of a kidney cell culture, and EGF, the product of submaxillary gland culture, would utilize the cell electrophoresis, tissue culture and protein electrophoresis systems; beta cells would either be the product of the electrophoretic separation of numerous minced human pancreata or the product of a pancreas cell tissue culture and its subsequent cell electrophoresis. Interferon is contained in a lymphocyte tissue culture medium which would use the protein electrophoresis system for separation. Definition of a processing system to produce these products would provide a true multiproduct system evaluation.

These six products were further evaluated to determine total market potential, market risk, and the target market for each. These results are summarized in Figure 5. AHF was determined to have a market for about 500×10^6 units per year. It was estimated that at best, 30% of this market could be captured by the space processed material. Purity requirements for those hemophiliacs suffering antigenic reaction to current preparations, and probable reduction of hepatitis were major considerations. These were partially offset by the expected higher cost of space processing. The ESF market was somewhat more difficult to determine since the product is not currently available commercially; however, it was estimated that 7.0×10^9 units annually would be necessary to treat the anemia secondary to diseased kidneys. An arbitrary value of 30% of the market was targeted for space processing. Beta cells have the potential of curing diabetes

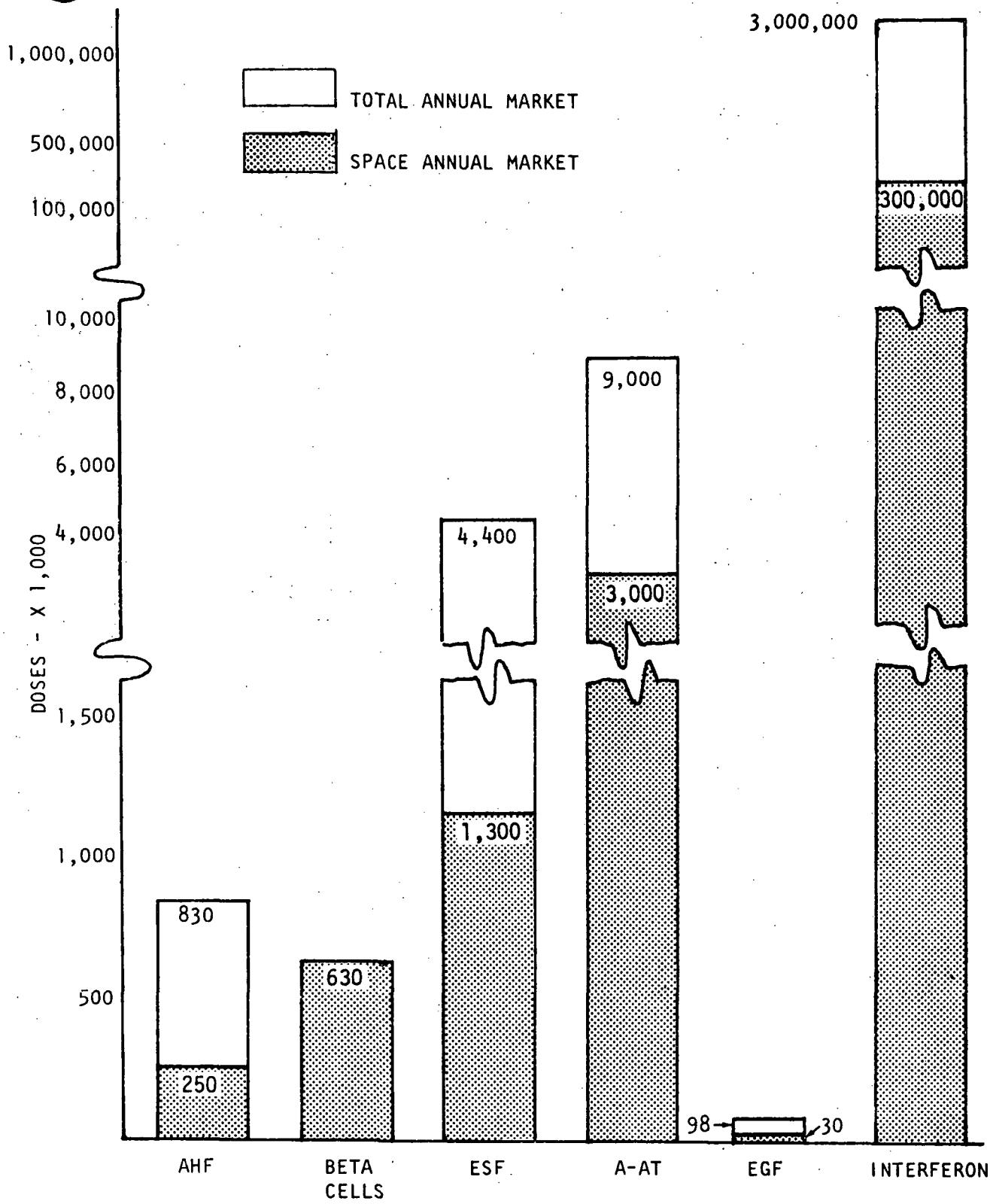


Figure 5. Annual Market

mellitus and thus would primarily be a single, total market rather that an annual requirement. It was projected that five years might be necessary to eradicate this disease. Subsequent requirements would only be for those newly contracting this disease. This market was projected to be 630,000 doses/year for five years followed by an annual need for 150,000 doses to cure new onsets.

The epidermal growth factor market is very difficult to estimate because the dosage and treatment regimen has not been established. It was estimated that 2.6 kg of EGF would be required annually to treat only 30% of the anticipated annual market of 14,000 burn patients. On the other hand 26,400 kg of A-AT would be required annually to meet the needs of 100,000 emphysema patients. Only 30% of this market is expected to be achieved by space processing, however, because of both the possible competition from ground processing after the market is developed and the reluctance of physicians to give long term prophylactic treatment to patients with no immediate overt difficulties. There is a current annual requirement for 6.6×10^{15} units of interferon. Because current ground production is 3×10^{11} units with heavy competition to develop new production techniques, we have estimated that space production would achieve only 10% of the market.

Of the six products subjected to detailed market analyses, three were chosen to serve as model products. These products were antihemophilic factor VIII, beta cells, and erythropoietin. All six products were used for the development of requirements for a multiproduct processing system; the three model products were used to exercise the conceptual system and assess developmental feasibility.

5.0 PROCESS SYSTEM REQUIREMENTS

The purpose of this task was to assess the requirements for a multiproduct production facility to produce three "model" pharmaceutical products selected from those studied in the task regarding product requirements and analysis. Such a facility must be in conformance with good manufacturing practices imposed by the Food and Drug Administration either as written or with appropriate modifications for space processing. Therefore, with the aid of a participating pharmaceutical company, contact was made with the FDA to start exploratory discussions of the space bioprocessing concept, the candidate substances considered for production and the applicable governing regulations. This agency was very cooperative and appreciative of being brought into our program at the conceptual stages. Agency guidance will be continued through meetings with representatives from the divisions they consider pertinent to this concept. These governing regulations were previously reviewed by us and the results are summarized in Figure 6. Modifications were recommended in several areas. Where the operators and supervisors were required to have sufficient experience and training, qualifying statements were added to permit spacecraft crew operations and ground supervision. The requirements on facilities and equipment require modification to allow onboard irreversible (nonretrievable) storage of waste, recycling of some materials, and the potential for remote operation and monitoring of automatic processing systems. These FDA representatives could see no insurmountable problems with regard to space bioprocessing as outlined by us.

Our approach to establishing process requirements was to evaluate current ground processes for three products to determine required process functions. Erythropoietin is now produced commercially in limited amounts from plasma of anemic sheep, while researchers use the urine of aplastic anemic humans as a source. The erythropoietin in either case is separated by precipitation techniques. Beta cells are obtained from minced human pancreatic tissue using an enzymatic digestion process followed by density gradient separation. Antihemophilic factor is separated from human plasma by protein precipitation. Therefore, the minimum requirement for space production of these pharmaceuticals from natural materials is the ability to separate cells and proteins from unwanted constituents in a mixture. In addition, production of desired cells or protein products can probably be enhanced by cell culture of selected strains.

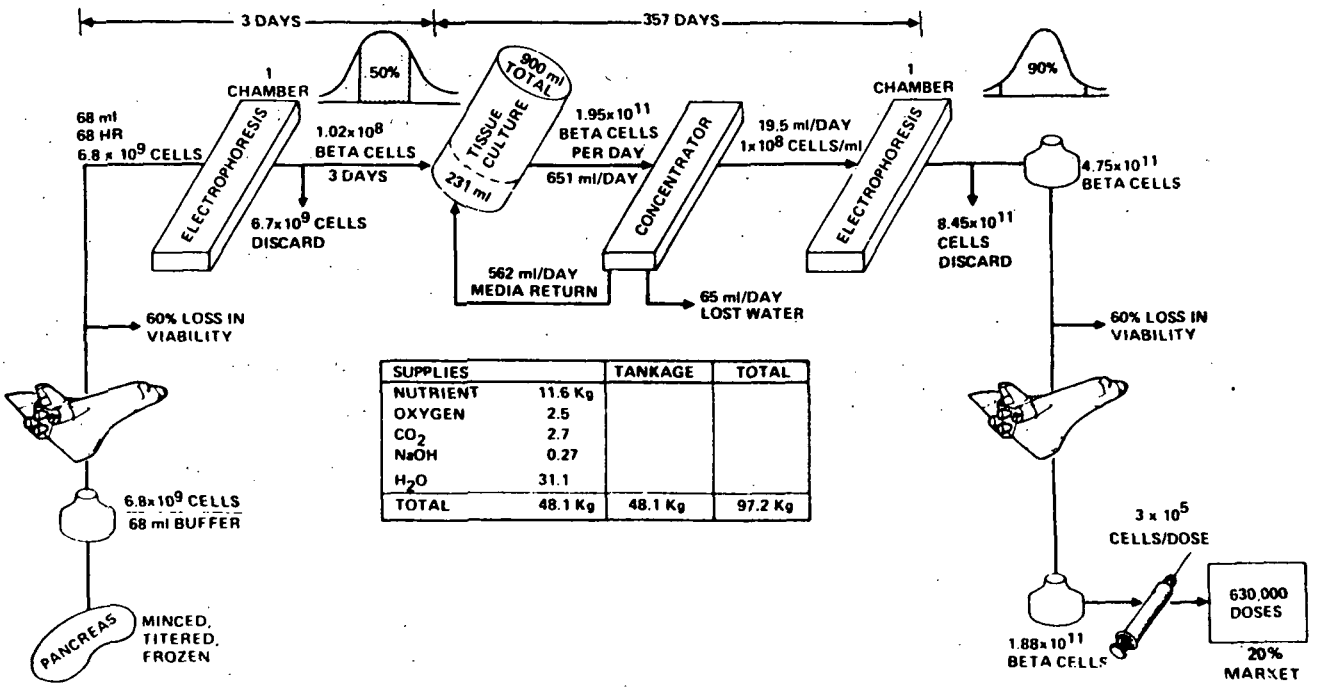
PARA.	SUBJECT	MODIFICATION
211.10	GENERAL PROVISIONS	ALLOW REMOTE MONITORING BY RESPONSIBLE PERSONNEL
211.10	FACILITIES	ALLOW VARYING LOCATION; IRREVERSIBLE ON BOARD WASTE STORAGE
211.30	EQUIPMENT	ALLOW FLUID RECLAMATION
211.40	PRODUCTION AND CONTROL PROCEDURES	ALLOW AUTOMATIC CONTROL WITH REMOTE MONITORING
211.42	COMPONENTS (CONSTITUENTS)	REMOVE VISUAL EXAMINATION, ALLOW RECLAMATION OF COMPONENTS FOR MULTIPLE PRODUCTS

Figure 6. Good Manufacturing Practices Modifications (Part 211, Title 12 Chapter 1, 1977)

Our method of choice for cell and protein separation is continuous free flow electrophoresis. Large scale commercial application of this technique for ground processing is restricted due to the effects of gravity in limiting throughput and resolution. It is anticipated that minimizing thermal convection and sample velocity variations by operating in microgravity will significantly aid electrophoresis. The improvement in the throughput was estimated to be about two orders of magnitude for both cells and proteins.

Improved separation of cells may allow the culturing of selected strains to greatly increase pharmaceutical production. Separation of high yield cells from human kidney tissue and subsequent culture would be superior to either sheep plasma or human urine as a source for erythropoietin. This protein hormone would then be separated from the culture media by electrophoresis. For beta cell production, the tradeoff between electrophoresis of human pancreatic tissue alone, or its electrophoresis and subsequent cell culture, is in favor of electrophoresis and culture at relatively low throughput. Assuming significant culture of beta cells can be developed, electrophoresis would then be used to separate beta cells for a high yield, almost pure culture.

Evaluating the process for space production of the three selected "model" products requires the evolution of mass flow rates and capacities for the equipment required for the process. A schematic of a typical mass flow balance for the space production of pancreatic beta cells is shown in Figure 7. The use of the mass balance concept forces a delineation of what must be accomplished in the process for each product in a stepwise fashion. The depicted quantities of materials at each step will quickly determine if the process is feasible with current technology, where areas of information must be obtained to fill in the gaps, and the anticipated recurring transportation costs to haul the material to and from space. While it does not define the total cost of the system, it does give the prospective manufacturer and NASA a general idea of the size, power and weight of the processing equipment as well as the extent and type of utilities and storage requirements. The length of the missions will be defined to determine economic feasibility. This has to be interwoven with the NASA program and schedules to determine if, and when, a vehicle capability will be available to support such a manufacturing facility.



SUPPLIES		TANKAGE	TOTAL
NUTRIENT	11.6 Kg		
OXYGEN	2.5		
CO_2	2.7		
NaOH	0.27		
H_2O	31.1		
TOTAL	48.1 Kg	48.1 Kg	97.2 Kg

Figure 7. Space Production - Beta Cells

These mass balances were defined for three cases with each product: space production, ground production, and one alternative combination of space and ground production. These possibilities were compared using space transportation cost as opposed to quantities of electrophoresis chambers required for ground processing modes. The results of this comparison are shown in Figure 8. With antihemophilic factor separation from cryoprecipitate, the advantages of space separation are obvious. For a transportation cost differential of 3.4\overline{M}$ the complexity and cost of 3878 chambers required for separation on the ground is reduced to that of 20 chambers in space. This cost is also a relatively small fraction of the 25.8\overline{M}$ value of the separated products. For beta cells, the product value is much higher at 100\overline{M}$, based on equivalent insulin injections, however, the amount of product and the scale of the process is smaller. Again, there is a large reduction in the number of electrophoresis chambers required favoring space processing. For erythropoietin production, the small amount of hormone product in the culture media required both large scale cell culture and electrophoresis. The large scale favors ground culture; however, the large number of chambers (23,042) required for ground separation favors a space separation/ground culture combination. Erythropoietin process requirements make it much less desirable as a product for the multiproduct production system than either beta cells or antihemophilic factor.

PRODUCT	CULTURE SIZE	ELECTROPHORESIS CHAMBERS	TRANSPORTATION (SUPPLIES ONLY)
AHF/CRYOPRECIPITATE (25\overline{M}$ VALUE)			
GROUND	N/A	3878	
SPACE	N/A	20	3.4\overline{M}$
BETA CELLS ($100M VALUE)			
GROUND	0.8L	27	
SPACE	2.0L	1	0.05\overline{M}$
GROUND/SPACE	5.0L	31	0.03\overline{M}$
ERYTHROPOIETIN			
GROUND	375L	23042	
SPACE	375L	115	18.7\overline{M}$
GROUND/SPACE	433L	1089	$ 8.2$\overline{M}$

Figure 8. Space Production Benefit Comparison

Consequently, erythropoietin was included in the subsequent requirements analysis for a multiproduct space processing system only to provide a capability for applied research on the material.

Based on the mass balance analyses done on the three products, a multiproduct production system shown in Figure 9 would be capable of satisfying 30% of the potential market for antihemophilic factor VIII and 20% of the potential beta cell market per year. In addition, it could be used for trial runs of erythropoietin production to see if it would be improved as a space processed product candidate. The two liter culture vessel and supporting system would be used for culturing beta cells or erythropoietin producing cells, separated by electrophoresis from human pancreatic or kidney cells, respectively. After culture, the beta cells would be separated from lysed and unwanted cells, rate frozen, and stored in a freezer. Erythropoietin would be separated from concentrated culture media, analyzed, lyophilized, and stored. For antihemophilic factor production, reconstituted cryoprecipitate would undergo electrophoresis, analysis, lyophilization, and storage.

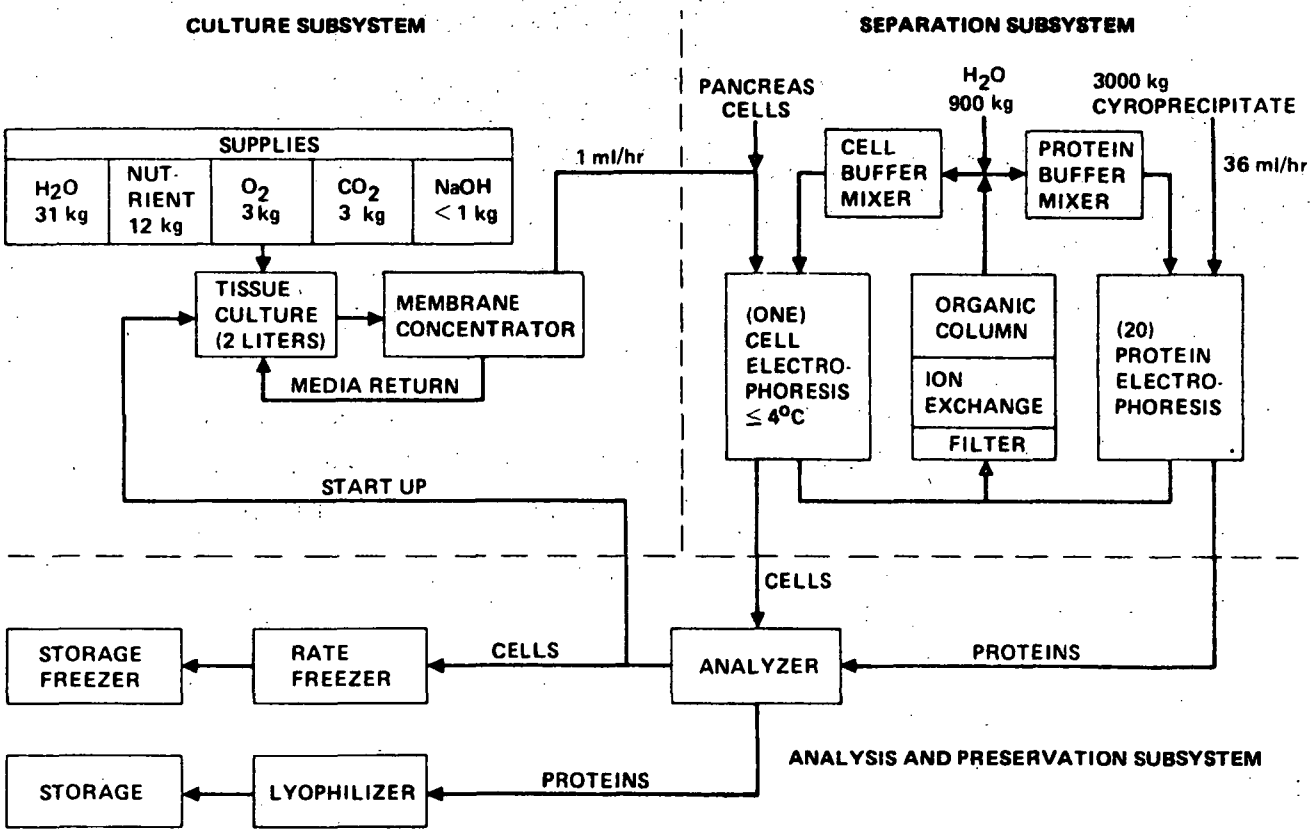


Figure 9. Multi-Product Process System

At a subsequent time in the study, three additional products were "processed" through the system to see if any modifications to the concept were required. Except for minor changes in chemical constituents and instrument settings to create a more compatible environment for each candidate product, the hardware is designed and sized as a truly multiproduct production system. The mass balance concept should be applied to other classes of products in future studies to determine if they also are compatible with the size of the system.

6.0 LESSONS LEARNED

During this study a number of lessons have been learned about obtaining and fostering commercial producer participation in studies of space processing. These should be given due consideration in formulating plans for future studies of this nature. They are presented here in brief, and MDAC-St. Louis recommends that they be adopted as elements in the NASA model for exploring other market sectors considered for the commercialization of space.

The key to involving industry in space processing is to establish a fully business-like footing for their participation. In most cases, the producer industry is relatively unfamiliar with the space environment, operations in space and the requirements and techniques of designing and integrating systems hardware to be flown in space missions. Dealing directly with NASA would involve them in a new form of governmental interface to which they are not accustomed.

By establishing a buffer team between itself and the industry with which it desires to build participatory agreements, NASA can establish the businessman-to-businessman relationship so essential to nurturing commercial enterprise in space. The aerospace company chosen for the buffer team should have established a competence in dealing with the particular process NASA wishes to advance as a candidate for production operations in space. Moreoever, the company should have made a significant commitment on its own, in terms of funds and manpower, to the development of that process before NASA chooses that firm to serve on the buffer team. The buffer team should also include an independent business analysis firm specializing in the particular industry to be approached. The right business analysis firm not only knows the industries of interest, but is familiar with the particular environment in which the producers operate. It has access to business documentation resources beyond the aerospace horizon; and, most importantly, such a firm will know key management and technical personnel of these companies plus the correct business basis on which to approach them.

The candidate producer firms identified by the buffer team should be subjected to a penetrating business analysis by the business consultant member of the team. This analysis should include such factors as: the firm's annual sales and growth;

the size of the company; the new products it has marketed; the tenure of the firm's senior officers; the surplus funds available for investment; the size of the firm's R&D budget; and the identifiable constraints on the firm's growth. In addition, there will be factors requiring evaluation which are peculiar to the specific class of industry being approached.

Having made contact with the companies by introductory letter, follow-up telephone calls should arrange for a formal presentation at the producer's own facility. After establishing a degree of rapport with their business or technical management, the presenting company should tailor each presentation to the interests of the key people in each producer company, i.e., the corporate decision makers and senior technical personnel.

Personnel making the presentation should be thoroughly familiarized with the segment of industry they will be visiting; at least one member should have credible experience in that producer industry. All members should be prepared to speak the vocabulary distinct to that industrial field of endeavor. The presentors should be a systems team that is capable of addressing all aspects of space processing to the audience's satisfaction. Not only must they be knowledgeable in the area of products and processes, but also familiar with space flight systems and how day-to-day activities in space are carried out. They must be thoroughly prepared, as well, to discuss resource requirements, costs and manpower, and schedules. Inclusion of a life sciences specialist in the team is highly desirable so that questions on man's contributions and requirements in space can be answered.

The presentation approach should reflect the businessman-to-businessman relationship desired between the buffer team and the manufacturing firm. It must reflect that industry is profit oriented rather than knowledge oriented; research must ultimately lead to increased corporate profit. By selecting products of particular interest to that company and presenting relevant market and business forecasts, a profit potential can be demonstrated in a way to engage both the technical and management attention of the audience. Using a conservative approach in the presentation, especially with technical and business values familiar to the audience, will give individuals an excellent chance to contribute to the discussions and to realize that their experience and participation would greatly enhance the program.

In this situation, the presentation approach should reflect that a joint working arrangement between the visited company and the aerospace industry would be mutually beneficial, using the strengths of each partner to achieve new goals. It must convey the attitude: "We are deeply involved and would like you to join us" rather than "You tell us what we can do for you in space." If the presentation features working hardware, mathematical analyses and models, as well as preliminary product data with their related market and risk analyses, the audience will feel that the presenters have a strong corporate investment in the concept, both financially and in terms of manhours of effort.

During the presentation, the question is invariably asked of the presentor, "Why should we manufacturers be interested in space processing?" Placing a good reason for their interest early in the presentation can forestall the inquiry. The reason can easily be developed by identifying the visited company with a candidate product that has the potential of being produced in space and that also complements their already existing product line. We have found it is also essential to indicate very early in our presentations that the products discussed are of the very low volume-very high value type. Many of the proprietary pharmaceutical companies think in terms of large volume-low cost products which are not applicable in the space operations we visualize.

Results of the presentations will develop relatively slowly. The companies visited will take time to digest what is presented and investigate the claims made. Experience in this study has shown that this phase will take about three months. If results of the initial investigation are favorable, the company will present the concept to their corporate management. This second phase usually will take two more months. The formal development of participating documentation (e.g., protocols, agreements, etc.) and approval of budgets will ordinarily consume an additional six to twelve months. All during this time, routine contact between the two companies should be maintained with pertinent management and technological data exchange by both sides as required.

During this period, it is extremely important not to exploit the manufacturing company names or the products they have under consideration. If such information

became generally known without the consent of the candidate participant, cooperation would probably be terminated. The privacy of a manufacturing company considering participation must be respected until the firm decides to announce publicly, for itself, its intent to participate in the exploration of space applications.

A data base concerning a potentially profitable candidate product must be developed upon which a technology interchange can be established between the interfacing company and the candidate producing company. Cooperative laboratory activities are essential tools in building the required data base. In this way MDAC-St. Louis established a technology interchange with the participating pharmaceutical companies. This, in turn, we believe, has enhanced the level of interest of these companies in the potential offered by processing pharmaceuticals in space.

Many potential products can be proposed for space processing by reviewing the literature and discussing the subject with professionals in the field of interest. Many of the suggestions may be of interest scientifically for their own sake but will have little chance of being rapidly adopted by the workers in that field if they offer no substantial improvement over existing materials. If the companies do not see a significant return on their investment in research and development of a product they will ignore that product.

Development of market data on products important to candidate participating firms is a key to securing their interest. A search of the literature, supplemented by consultations with clinical authorities will provide the information necessary to develop a picture of the current market open for the model products. Reasonable assumptions, based on the guidance of clinical research teams, will yield use market projections for advanced clinical uses. Finally, appropriate business risk analysis should be employed to assess the market risks for processes and products as they move from initial R&D commitment through ground and flight experimentation to achieve successful flight production demonstrations. By offering these preliminary analyses to prospective participators, much useful data can be obtained during the presentation itself. Most important, the potential participating firms will be assured that the presentor has a business understanding and an investment attitude appropriate for cooperative endeavors for their mutual benefit.

A hardware system that is capable of producing a variety of products with only minor operational changes, e.g., instrument settings and chemical substrates, would offer significant operational, logistics and cost advantages to a producer. Using conservative assumptions based on data from the literature, tempered by laboratory experience, the requirements for such a system can be developed and its significant operating characteristics can be defined. This was the approach used by MDAC-St. Louis to define a system for processing pharmaceuticals in space. All of the twelve biological products reviewed in this study could exercise the system in part, or in its entirety, thus supporting the concept of a true multi-product system.

While this study was done to assess the commercial feasibility of manufacturing pharmaceutical products in space, it serves as a model for those who wish to consider other processes or products in the same environment. The use of the mass balance analytical concept forces a delineation of what must be accomplished in the process for each product in a stepwise fashion. The calculated quantities of materials at each step will quickly determine if the process is feasible with current technology, where the areas of information must be obtained to fill in the gaps, and anticipated recurring transportation costs to haul the material to and from space. While it does not define the total cost of the system, it does give the prospective manufacturer and NASA a general idea of the size, power and weight of the processing equipment as well as the extent and type of storage requirements. The length of the missions will be defined to determine economic feasibility. This will have to be interwoven with the NASA program and schedules to determine if, and when, a vehicle capability will be available to support such a manufacturing facility. Legal and regulatory considerations will also have to be defined.

Recommendations for future work are presented in Figure 10. It is recommended that drug firm involvement be continued and encouraged both in ground research and product evaluation. Because of companies' sensitivity about government interference and disclosure of trade secrets, each company should be dealt with on an individual basis with some other private firm serving as a buffer or interface between the individual companies and the government. Heavier involvement through evolutionary processes will probably lead to direct participation in space activities. Such participation will logically require a user development laboratory for these companies' product developments.

- CONTINUE USER INVOLVEMENT
  - GROUND RESEARCH
  - PRODUCT EVALUATION
- INDIVIDUAL DEALINGS WITH DRUG COMPANIES
  - SENSITIVE ABOUT GOVERNMENT INTERFERENCE
  - CONCERNED ABOUT TRADE SECRETS
- MOVE TOWARD USER PARTICIPATION IN SPACE ACTIVITIES
  - USER DEVELOPMENT LABORATORY FOR PRODUCT DEVELOPMENT
- EXAMINE EQUIPMENT SIZE AND COST
- DEVELOP MASS BALANCES FOR EACH NEW PRODUCT CONSIDERED

Figure 10. Recommendations